REMARKS/ARGUMENTS

Claims 1 to 66 were previously pending in this application. With this Amendment and Response Applicants have cancelled claims 1 to 7, withdrawn claims 8 to 66 and added new claims 67 to 77. No new matter has been added with these amendments.

Remarks on Restriction Requirement

In the Examiner's first action, it was indicated that Applicants would have to restrict the claims between one of the following four inventions: SUMOylation blockers, deSUMOylation enhancers, Ubiquitination activators, and deUbiquitination inhibitors. Although Applicants do not dispute the Examiner's separation of the SUMOylation agents and the Ubiquitination agents, Applicants do respectfully traverse the Examiner's further separation of these agents into the blocker and the enhancer.

Specifically, contrary to the Examiner's position these agents do operate on the same molecule, namely small ubiquitin-related modifier-1 or SUMO-1. Moreover, they have the same functional effect, to reduce protein SUMOylation. However, Applicants do understand that the originally filed claims improperly separated these and provided no generic claim upon which the Examiner could properly search. Accordingly, Applicants have cancelled the original claim set and inserted a new set of claims of which the broadest independent claim recites:

> A method of treating neurodegeneration in a patient, comprising
> identifying a patient diagnosed with neurodegeneration; and
> administering to the patient a therapeutically effective amount of an agent for reducing protein SUMOylation.

This new claim provides a generic claim under which both the SUMOylation blockers and the deSUMOylation enhancers of the current invention would fall. Further, this claim is fully supported by the application that states the goal of the invention in the following section of the specification:

> Long repeats of polyglutamines within specific disease genes are responsible for at least eight human neurodegenerative diseases,

including Huntington's disease (HD). Expression of a truncated portion of the mutant Huntington protein encoded by exon 1 of the *HD* gene (Httex1p) causes neurodegenerative disease similar to HD in transgenic mice and flies. SUMO-1 (small ubiquitin-related modifier-1) modification of proteins affects their stability, protein-protein interactions, and/or subcellular localization. Httex1p was found to be SUMO-1 modified and ubiquitinated. Mutation of three lysine residues in the amino-terminal 17 amino acids of expanded Httex1p to arginine (K6R, K9R, and K15R) reduces stability of this polypeptide in cell culture. In mutagenesis studies, lysines 6, 9, and 15 were found to be important for SUMOylation of Httex1p and ubiquitin and SUMO-1 may compete for lysines 6 and 9. PML SUMOylation is reduced in HD transgenic mouse brain. Since in polyQ disease brains, nuclear body morphology is changed, a reduction in SUMOylation of PML may be instrumental in the disruption of nuclear body structure. Expanded polyQ Httex1p co-localizes with PML and SUMO-1 in nuclear bodies in transgenic mouse brain and in cell culture, consistent with many nuclear body proteins found to be modified by SUMO-1. Crossing a *Drosophila* model of HD with a reduced function *smt3* (*Drosophila* SUMO) mutant results in suppression of lethality and of neurodegeneration of photoreceptor neurons in the eye. Therefore a drug therapy designed to lower SUMOylation in the cell, or increase cleavage of SUMO-1 from target proteins such as Htt, should be useful to destabilize Httex1p and block neurodegeneration in HD and other polyQ diseases.

(Specification, page 12, line 17 to page 13m, line 15, underlining added for emphasis.)

In short, Applicants invention is directed to a method of treating neurodegeneration by reducing protein SUMOylation. This protein SUMOylation reduction can be carried out either by blocking SUMOylation or enhancing

deSUMOylation, but both provide the same functional effect on the same molecule, and accordingly should not be considered different inventions, but at most different species of the same broader invention.

In light of these amendments Applicants would respectfully submit that all of the new claims 67 to 77 relate to the same invention, and therefore should be the subject of the same patent examination.

Statutory Election

Pursuant to Applicants' statutory requirement to provide an election, should the Examiner not agree with the above remarks, Applicants' hereby elect to pursue Invention II and neurodegenerative disease species (G).

Conclusion

In view of the foregoing amendment and response, it is believed that the application is in condition for allowance and, accordingly, reconsideration and allowance is earnestly solicited.

If any questions remain regarding the allowability of the application, Applicant would appreciate if the Examiner would advise the undersigned by telephone.

The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 and 1.17 which may be required by this paper to Deposit Account No. 03-1728. Please show our docket number with any charge or credit to our Deposit Account.

Respectfully submitted,

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